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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,674	08/09/2001	Suzanne Cory	11686A	3390

7590 11/03/2003

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,674	CORY ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-20* is/are pending in the application.

4a) Of the above claim(s) *11-17,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *6-10 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 August 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/155,327* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

► Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (*http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm*). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306.**

Election/Restrictions

Applicant's election with traverse of Group I. Claims 6-10 and 18 in Paper No. 08/21/03 is acknowledged. The traversal is on the ground(s) that inventions are not independent and distinct. The applicant argues that in view of the continued increase of official fees and the potential limitation of applicant's financial resources the four-way restriction requirements may become prohibitive and thereby contravene the constitutional purpose to promote and encourage the purpose of science and the useful arts. The applicant argues that the classification system is also an unreliable basis for requiring restriction. This is not found persuasive because this restriction is in accordance with MPEP. The inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the modes of operation, functions, and/or effects of sense molecule is different from the modulatory function and effects of a ribozyme molecule. For example, a sense DNA molecule (Group II) could produce a transdominant negative gene product that competes with endogenous bcl-w, where as the ribozymes (Group III) effects the mRNA translation. In addition the method of group II and III does not requires the use of polypeptide (Group I) and antibody (Group IV), since polypeptides and antibodies are structurally and functionally distinct product. Thus, these inventions are mutually exclusive and are of separate use.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-17 and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 08/21/03.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The Preliminary amendment filed on 08/09/02 modified the nucleotide sequences of SEQ ID NO: 6 and SEQ ID NO:8 and Figure 9A and 9B of instant application which are not supported by priority documents US 09/155327 and AU PN8965. Specifically the applicant fails to point out where is the support for the changes made in the instant application in view of foreign priority document AU PN8965. The priority date of the instant application is 08/09/01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-10 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Guastella (US 5789201, 1998).

Instant claims are drawn to an isolated polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9 or a polypeptide encoded by the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 having 47% or greater similarity. In addition the claims are drawn to an isolated poly peptide encoded by a nucleic acid capable of hybridizing to the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 under low stringency condition and have having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9.

Guastella teaches nucleotide sequences encoding a bcl-2 homolog (bcl-y), which matches 98.2% to SEQ ID N0: 6 and 95.9% to SEQ ID NO:8. The cited art further teaches amino acid sequences which matches 99.5% to the SEQ ID NO:7 and 99.3% to SEQ ID NO:9 (see PTO sequence search report). In addition the cited art teaches that a functional derivative of disclosed bcl-2 polypeptide may or may not contain post-translational modifications such as covalently linked carbohydrate, depending on the necessity of such modifications for the performance of a specific function (col.4, line 67-). The cited art further teaches that "functional derivative" is intended to include the "fragments," "variants," "analogues," or "chemical derivatives" of a molecule (col.5, lines 1-6). The cited art further teaches the manufacturing of recombinant bcl-y or variants thereof which clearly encompasses the pharmaceutical composition of claim 18, since amino acid sequence disclosed in the cited prior is only 99.5% and 99.3% identical to the

claimed SEQ ID NO:7 and SEQ ID NO:9 respectively. Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-10 and 18 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses an isolated polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9 or a polypeptide encoded by the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 having 47% or greater similarity. In addition the claims are drawn to an isolated poly peptide encoded by a nucleic acid capable of hybridizing to the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 under low stringency condition and have having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9.

At best the specification only teaches isolated polypeptide (human and mouse bcl-w) comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID

NO:9 (encoded by SEQ ID NO:6). The specification as filed fails to disclose any variant of human or mouse bcl-w explicitly or implicitly that have bcl-w like activity.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only teaches the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification as filed fails to disclose any variant of that has the functional property of human or mouse bcl-w polypeptide explicitly or implicitly as putatively claimed herein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them

from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nucleic acid and/or amino acid variants (as claimed) has been defined only by a statement of function that broadly encompasses bcl-2 or bcl-w like activity, which conveyed no distinguishing information about the identity of the claimed nucleic acid or amino acid sequences, such as its relevant structural or physical characteristics. The variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of a bcl-2 like polypeptide. In addition 53% variation (47% identical) as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 6-10 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polypeptides comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6), does not reasonably provide enablement for any variant or derivative of an isolated polypeptide (bcl-w) consisting of amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of Invention:

Invention relates to a polypeptide or variant thereof that belongs to bcl-2 family.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses an isolated polypeptide having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9 or a polypeptide encoded by the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 having 47% or greater similarity. In addition the claims are drawn to an isolated poly peptide encoded by a nucleic acid capable of hybridizing to the nucleotide sequence as set forth in SEQ ID NO: 6 and SEQ ID NO:8 under low stringency condition and have having 47% or greater similarity to amino acid sequences as set forth in SEQ ID NO: 7 and SEQ ID NO:9. At best the specification only teaches isolated polypeptide (human and mouse bcl-w) comprising the amino acid sequences of SEQ ID NO: 7 (encoded by SEQ ID NO:6) or SEQ ID NO:9 (encoded by SEQ ID NO:6). The specification as filed fails to disclose any variant of human or mouse bcl-w explicitly or implicitly that have bcl-w like activity.

State of Art and Predictability

The stat of the art at the time of filing teaches that Bcl-2 family proteins play a central role in apoptosis regulation. The Bcl-2 family comprises various members which have very diverse functions. For example in humans over 20 members of this family have been identified, including proteins that suppress (Bcl-2, Bcl-XL, Mcl-1, Bfl-1/A1, Bcl-W) and proteins that promote (Bax, Bak, Bok, Bad, Bid, Bik, Bim, Nip3, Nix) cell death. Bcl-2 family proteins contain at least one of four conserved regions, termed Bcl-2 homology (BH)1 domains. Most members of this family also contain a TM domain located near their carboxyl terminus that anchors them in intracellular membranes of mitochondria and other organelles. Many Bcl-2 family proteins are capable of physically interacting, forming homo- or heterodimers, and functioning as agonists or antagonists of each other. Specificity for interaction partners and tissue-specific patterns of expression combine to endow each mammalian Bcl-2 family protein with a unique physiological role *in vivo*, resulting for example in highly diverse phenotypes when members of this multigene family are individually knocked out in mice. Thus, a need exists to identify comprehensively the members of the Bcl-2 family and to elucidate their functional characteristics (Ke at al, J. Biol. Chem., 276(16):12481-12484, 2001). In instant case considering the scope of variation as claimed *(53% variation, which also encompasses conserved motifs)*, it is highly unpredictable that variants as claimed would have any bcl-2 like activity. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited variants are mere hypothetical scenarios, since no biological functions have been established for the claimed variants. The mere

identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). In addition considering the applicants disclosure and the state of bc-2 family art it is highly unpredictable that one skill in the art would be able to use the variants as claimed as a pharmaceutical composition to treat any disease without undue experimentation. Therefore, applicant has not presented enablement commensurate in scope with the claims.

Undue Experimentation:

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case screening of any and all natural and non-natural variants, wherein 53% of amino acid are added substituted and /or deleted in the disclosed SEQ ID NO:7 and 9 is not considered routine in the art. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 53% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed bcl-2 and/or bcl-w like-activity. This is not considered routine in the art and the experimentation left to those skilled in

the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER